

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761143Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRM)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	BLA
<b>Application Number</b>	761143
<b>PDUFA Goal Date</b>	March 6, 2019
<b>OSE RCM #</b>	2019-1484
<b>Reviewer Name(s)</b>	Courtney Cunningham, PharmD
<b>Team Leader</b>	Laura Zendel, PharmD
<b>Division Director</b>	Jamie Wilkins, PharmD
<b>Review Completion Date</b>	January 15, 2020
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Teprotumumab-trbw
<b>Trade Name</b>	Tepezza
<b>Name of Applicant</b>	Horizon Pharma Ireland, Ltd.
<b>Therapeutic Class</b>	Human monoclonal antibody; insulin-like growth factor-1 (IGF-1R) inhibitor
<b>Formulation(s)</b>	Intravenous infusion
<b>Dosing Regimen</b>	Starting dose 10 mg/kg dose 1, if tolerated, increase to 20 mg/kg once every 3 weeks for a total of 8 doses

## Table of Contents

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EXECUTIVE SUMMARY .....	3
1 Introduction .....	3
2 Background .....	3
2.1 Product Information .....	3
2.2 Regulatory History.....	4
3 Therapeutic Context and Treatment Options .....	4
3.1 Description of the Medical Condition .....	4
3.2 Description of Current Treatment Options .....	5
4 Benefit Assessment .....	6
5 Risk Assessment & Safe-Use Conditions .....	8
5.1 Embryo-Fetal Toxicity in Humans .....	9
6 Expected Postmarket Use.....	9
7 Risk Management Activities Proposed by the Applicant.....	10
8 Discussion of Need for a REMS.....	10
9 Conclusion & Recommendations.....	10
10 Appendices .....	11
10.1 References .....	11

## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the biologic teprotumumab-trbw is necessary to ensure the benefits outweigh its risks. Horizon Pharma Ireland, Ltd. (Horizon) submitted a Biologics Licensing Application (BLA 761143) for teprotumumab-trbw with the proposed indication of the treatment of thyroid eye disease. The most serious risk associated with teprotumumab-trbw includes potential embryo-fetal toxicity. Horizon did not submit a proposed REMS with this application to mitigate this risk.

Division of Risk Management (DRM) and the Division of Transplant and Ophthalmology Products (DTOP) agree that a REMS is not needed to ensure the benefits of teprotumumab-trbw outweigh its risks. Expectant cynomolgus monkeys given teprotumumab-trbw experienced numerous fetal abnormalities. However, upon analysis, the clinical review team has concluded that neither the data submitted by the Applicant nor the current literature supports a contraindication for use or notation in the warnings and precautions of the labeling at this time.<sup>1,2</sup> Therefore, the risk of potential embryofetal toxicity associated with teprotumumab-trbw will be communicated through labeling in Sections 8.1, 8.3, Section 17, and in the Highlights.

## 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) teprotumumab-trbw (teprotumumab-trbw) is necessary to ensure the benefits outweigh its risks. Horizon Pharma Ireland, Ltd. (Horizon) submitted a Biologics Licensing Application (BLA 761143) for teprotumumab-trbw with the proposed indication of the treatment of thyroid eye disease. This application is under review in the Division of Transplant and Ophthalmology Products (DTOP). The Applicant did not submit a proposed REMS with this application.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Teprotumumab-trbw, a fully human immunoglobulin monoclonal antibody (mAb), is an insulin-like growth factor-1 receptor (IGF-1R) inhibitor. The Applicant proposes teprotumumab-trbw for the treatment of active thyroid eye disease (TED). As TED involves the autoimmune activation and proliferation of orbital fibroblasts by signaling through the IGF-1R and thyroid stimulating hormone receptors, it is proposed that blocking these receptors will block the pathophysiologic signaling complex involved in TED. The application was granted orphan, fast track, and breakthrough designations by the Agency for the treatment of active TED.

Teprotumumab-trbw is proposed to be available as a sterile, preservative-free lyophilized powder packaged for reconstitution with 10 mL sterile water for injection. The solution is then diluted in 0.9% w/v sodium chloride prior to administration by a medical professional in an infusion center or hospital. The initial intravenous infusion is dosed at 10 mg/kg then increased to 20 mg/kg if tolerated. A total of 8

infusions, one every 3 weeks, are infused over 90 minutes for the first 2 doses, and if tolerated, infusion time can be shorted to 60 minutes. Teprotumumab-trbw is currently not approved for use in any other jurisdiction.

## **2.2 REGULATORY HISTORY**

The following is a summary of the regulatory history for teprotumumab-trbw (BLA 761143) relevant to this review:

- **05/06/2013:** Agency granted Orphan Drug designation.
- **03/09/2015:** Agency granted Fast Track Designation
- **07/29/2016:** Agency granted Breakthrough Therapy Designation for active TED
- **05/14/2019:** Pre-BLA meeting held to discuss Phase 3 trials, Advisory Committee, and Safety Updates.
- **07/08/2019:** BLA 761143 submission for TED received
- **11/06/2019:** A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for teprotumumab-trbw.
- **12/13/2019:** Dermatologic and Ophthalmic Drugs Advisory Committee Meeting was convened to discuss the efficacy and safety of teprotumumab-trbw. The AC voted 12/0 in favor of approval. A REMS proposal was not discussed.

## **3 Therapeutic Context and Treatment Options**

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### **3.1 DESCRIPTION OF THE MEDICAL CONDITION**

Thyroid eye disease (TED) is a rare, serious autoimmune disease that may lead to blindness. While most commonly associated with Grave's hyperthyroidism, TED may also affect those with other thyroid diseases such as Hashimoto's thyroiditis and those in euthyroid states. TED is caused by the activation and proliferation of orbital fibroblasts by signaling through IGF-1R and thyroid-stimulating hormone receptors (TSHR).<sup>3</sup>

TED occurs more commonly in women than men (16/100,000 versus 3/100,000), with a median age of diagnosis being 43 years of age. The annual US prevalence of TED is 75,000 patients. There is no predisposition based on ethnicity, but risk factors include smoking and family history of TED.

TED is divided into 2 stages; the "active phase," which involves a progressive worsening of symptoms and visible inflammation followed by an "inactive phase" that is characterized by no further deterioration in patients' conditions.<sup>4</sup> In the active phase of TED, patients present with proptosis, periorbital inflammation, diplopia, pain, eyelid retraction, and strabismus. These symptoms increase over time in the active phase, leading to an increase in eyelid aperture, a compromise in eye motility, diplopia, and in severe cases, dysthyroid optic neuropathy. Excessive proptosis may impair the ability to

close the eyes, causing pain and potential corneal ulceration and sleep deprivation. Approximately 6% of TED patients have their sight threatened by TED. This phase of the disease lasts 1 – 3 years.

In the inactive phase of TED, there is an absence of inflammation, but the significant remodeling and expansion of orbital tissue is still evident. Patients rarely return to their baseline, however, once TED has reached the inactive phase, it is unlikely to return to the active phase.

Severity of TED is distinct from, but related to, disease activity. Severity of TED is best defined by functional or cosmetic impairment, which can be assessed by various criteria, such as is the Clinical Measures of Severity based on the European Group on Graves' Orbitopathy (EUGOGO) Consensus Statement. Clinical activity of TED is commonly measured by the Clinical Activity Score (CAS). Both activity and severity should be considered in the treatment of TED, as the 2 measurements are not interchangeable and don't follow a linear relationship.<sup>5</sup>

### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

There currently are no FDA-approved medications or US based therapy guidelines to treat Active TED. The Consensus Statement of the European Thyroid Association (ETA)/European Group on Graves' Orbitopathy (EUGOGO) on the management of Active TED does advocate for some treatment approaches, most commonly corticosteroids. The use of corticosteroids to treat Active TED has both questionable efficacy and safety. Recently, there has been some experimentation with azathioprine, mycophenolate mofetil, cyclosporine, and tocilizumab for the treatment of Active TED. Orbital radiation serves as a second-line, nonpharmacologic therapy, and is used in the US only when corticosteroids are ineffective. Neither remodeling nor orbital tissue expansion is responsive to pharmacotherapy.<sup>6</sup>

Orbital decompression surgery is used only during inactive TED, typically as a sight-preserving therapy due to concerns that it may exacerbate any remaining inflammatory processes. It often involves several surgeries over the course of years to attempt to partially correct the remodeling.<sup>7</sup>

## 4 Benefit Assessment

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Two studies were used to determine the safety and efficacy for teprotumumab-trbw for active TED, TED01RV and HZNP-TEP-301. TED01RV (NCT01868997) was a Phase 2, 24-week, randomized, double-blind, placebo controlled, parallel group study. The 24-week treatment period began with a 10 mg/kg infusion, followed by 20 mg/kg for each subsequent infusion administered every 3 weeks for 8 total doses. A 48-week off-treatment follow-up period followed.

HZNP-TEP-301 (NCT03298867) was a Phase 3 trial with an identical study design as TED01RV. Proptosis non responders (study eye had < 2 mm decrease in proptosis) at Week 24 of the study, or those who relapsed during the 48-week follow-up were eligible to enroll in an open-label extension study, HZN-TEP-302 (NCT03461211) following the same 24 week treatment period followed by a 48-week follow-up period. The follow-up period for HZN-TEP-302 is ongoing, therefore, study HZN-TEP-302 results have been incorporated into the safety data only. Study HZN-TEP-302 currently includes 46 subjects.

Subjects were required to be between the ages of 18 to 75 or 80 years of age, have a clinical diagnosis of Grave's disease with a CAS  $\geq 4$  on a 7-point score ( $\geq 3$  noting active TED), and be euthyroid or have mild hypothyroidism or hyperthyroidism at screening and during the study. Both studies included patients in Europe and the United States. The most severely affected eye was considered the "study eye." Proptosis measurements were performed with an Applicant provided exophthalmometer. The primary endpoint of study TED01RV was the overall responder rate as defined by the percentage of subjects with a reduction in proptosis  $\geq 2$  mm AND a decrease in CAS  $\geq 2$  points from baseline in the study eye, without deterioration (increase in proptosis  $\geq 2$  mm or increase in CAS  $\geq 2$  points) in the fellow eye at Week 24. The primary endpoint of study HZN-TEP-001 was the proptosis responder rate at Week 24 as defined by percentage of subjects with a  $\geq 2$  mm reduction from baseline in proptosis in the study eye without deterioration of proptosis (increase  $\geq 2$  mm) in the fellow eye. Secondary endpoints included subjects' mean change from baseline in CAS and quality of life scores. The results of the primary endpoints of both studies are shown in Tables 1 and 2 below.<sup>6</sup>

**Table 1** – Results of study TED01RV (Intent to Treat Population, Study Eye)

Endpoint		Placebo (N = 45)	Teprotumumab- trbw (N = 42)	95% Confidence Interval (CI)	P-Value
Primary	Protopsis Responder Rate at Week 24 N (%)	9 (20.0)	31 (72.1)	34.39, 70351	<0.001
	Overall Responder Rate at Week 24 N (%)	9 (20.0)	30 (69.8)		<0.001
Secondary	Diplopia Responder Rate at Week 24 n/N (%) <sup>a</sup>	10/31 (32.3)	27/38 (71.1)		< 0.001

<sup>a</sup> n/N is the number of subjects over the denominator of number of subjects with Baseline diplopia.



**Table 2** – Results of study HZN-TEP-301 (ITT Population, Study Eye)

Endpoint		Placebo (N = 45)	Teprotumumab- trbw (N = 42)	95% Confidence Interval (CI)	P-Value
Primary	Protopsis responder rate at Week 24  N (%)	4 (9.5)	34 (82.9)	58.89, 88.01	<0.001
	Overall Responder Rate at Week 24  N (%)	3 (7.1)	32 (78.0)		< 0.001
Secondary	Diplopia Responder Rate at Week 24  n/N (%)	8/28 (28.6)	19/28 (67.9)		< 0.001

As demonstrated in both studies, subjects treated with teprotumumab-trbw have a statistically significant difference in response rate compared to those treated with placebo. Teprotumumab-trbw also met all secondary efficacy endpoints in both studies with statistical significance over placebo except for the category “Mean change from Baseline in Quality of Life appearance subscale transformed score through Week 24” in Study TED01RV.

## 5 Risk Assessment & Safe-Use Conditions

The current safety information includes both studies used to determine efficacy, a 120-day safety update from HZN-TEP-302 as well as the follow-up period from HZN-TEP-301. The total number of subjects included in the safety population is 121. The overall incidence of treatment emergent adverse events (TEAE) was 83.5%. Among TEAEs that were considered related to study drug, those that occurred at least 4% more commonly in the teprotumumab-trbw group compared to the placebo group included muscle spasms (25% vs. 7%), nausea (17% vs. 9%), alopecia (13% vs. 8%), diarrhea (12% vs. 8%), and hyperglycemia (10% vs. 1%). Several subjects experienced serious TEAEs. There was one report of each of the following serious adverse events in teprotumumab-treated subjects; diarrhea, E.coli sepsis, inflammatory bowel disease exacerbation, pneumothorax, infusion related reaction, Hashimoto’s

encephalopathy, urinary retention, visual field defect, and life-threatening cerebral hemorrhage. There were no deaths of study subjects.<sup>8</sup>

Muscle spasms, diarrhea, and hyperglycemia were considered of special interest as pertaining to the study. After noting a 17.4 % rate of ear and labyrinth disorders after the 120-day safety update, it too was named as a TEAE of special interest. Additional adverse events of special interest include gastrointestinal disorder, infections, muscle spasms, hyperglycemia, and reproductive system and breast disorders in the teprotumumab-trbw treated group, the interpretability was difficult due to low number of trial subjects.<sup>2</sup> Infusion reactions, exacerbation of inflammatory Bowel Disease (IBD), and hyperglycemia will be reflected in the Warnings of the labeling.

## **5.1 EMBRYO-FETAL TOXICITY IN HUMANS**

According to the clinical reviewer, drug administration was associated with cessation of weight gain, decreased serum alkaline phosphatase, and thymic atrophy. Additionally, genetic toxicity and carcinogenicity studies were not conducted or considered necessary for approval. Further, there were no human pregnancies in the studies due to strict study protocols including pregnancy testing of females of reproductive potential at baseline and at each follow up visit, and the use of 2 forms of contraception during treatment and 180 days after the last infusion. Male patients with female partners of reproductive potential had to be surgically sterile or use a barrier contraceptive during treatment and for 180 days after last dose. Because of the lack of human clinical trial data, the clinical review team does not feel the risk of embryo-fetal toxicity should be noted as a contraindication or be listed in the Warnings and Precautions in the product's label at this time. Therefore, the clinical review team has no available data of teprotumumab-trbw's potential embryo-fetal toxicity in humans.<sup>2</sup>

This risk will be therefore be outlined in Sections 8.1 and 8.3 and a directive to begin appropriate contraception before starting teprotumumab-trbw therapy and continue contraceptive use until 6 months after the last dose of teprotumumab-trbw in the highlights of prescribing section of labeling. The risk will also be noted in section 17 in patient labeling, with a directive to counsel on appropriate contraception use.

## **6 Expected Postmarket Use**

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Teprotumumab-trbw is expected to be prescribed by endocrinologists with diagnosis and input from an ophthalmologist. It is expected to be used at infusion centers or hospitals. Prescribers should note when giving teprotumumab-trbw to females of reproductive potential or their partners and counsel accordingly regarding contraception and the potential risk of human embryo-fetal toxicity as outlined in the labeling.

## 7 Risk Management Activities Proposed by the Applicant

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The Applicant did not submit a proposed REMS with this application but did propose plans for post-marketing safety at the Advisory Committee Meeting on December 13, 2019. (b) (4)

(b) (4)

Further information regarding these activities has not been provided to the Agency at the time of this review.

## 8 Discussion of Need for a REMS

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The Clinical Reviewer recommends approval of teprotumumab-trbw on the basis of the efficacy and safety information currently available.

Teprotumumab-trbw met both primary and nearly all secondary endpoints for efficacy criteria in the treatment of thyroid eye disease. Additionally, the clinical review team has decided the indication should be TED, without additional qualifiers of active or inactive.

The commonly reported TEAEs were muscle spasms, diarrhea, hyperglycemia, alopecia, and ear and labyrinth disorders. Other AE's included infusion reactions and IBD. Additionally, in a trial of teprotumumab-trbw on pregnant cynomolgus monkeys, all fetuses born to those treated with teprotumumab-trbw at 8.8 times the recommended maximum human dose experienced defects. However, the effects on human fetuses and human breastmilk are unknown as there were no human pregnancies in teprotumumab-trbw trials. The studies were performed with small subject populations, the published literature mixed, and the human data unknown. As such, the clinical review team concluded that until postmarketing data demonstrates otherwise, teprotumumab-trbw does not warrant stronger risk management measures than labeling. Because of the lack of human data as submitted in the application as well as the published literature being mixed regarding IGF1R inhibition to affect fertility, the clinical review team will not include this as a warning or contraindication at this time. This potential risk will be communicated in Sections 8 and 17 of the labeling. will not include this as a warning or contraindication at this time.

## 9 Conclusion & Recommendations

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Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks of teprotumumab-trbw. The safety concern of potential human embryo-fetal toxicity associated with teprotumumab-trbw use will be communicated via labeling.

Should the Division of Transplant and Ophthalmology Products have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

## 10 Appendices

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### 10.1 REFERENCES

1. McDougal A, PhD. Pharmacology/Toxicology BLA Labeling Review and Evaluation of BLA 761143. January 10, 2020.
2. Chambers WM. Clinical Review of BLA 761143 (teprotumumab-trbw). January 13, 2020.
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7. Bartalena L BL, Boboridis K, et al. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy guidelines for the management of Graves' orbitopathy. *Eur Thyroid J*.5:9-26.
8. Horizon Pharma Teprotumumab Summary of Clinical Safety. 2019.

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